REMARKS

Claims 19-30 are pending. Claim 26 is amended herein without prejudice and without acquiescence, and the amendment finds support in the specification at page 4, lines 13-22 of the application as originally filed. No new matter is entered herein.

I. Priority

The Examiner states that the Applicant has not complied with the requirements of 37 CFR 1.63(c) because the oath, declaration, or Application Data Sheet (ADS) does not acknowledge the filing of any foreign application. Applicants submit a Supplemental ADS herewith.

The Examiner also states that Applicants have not complied with the requirements of 37 CFR §1.63(c) and that the foreign priority claim was not filed during the time period set forth in 37 CFR §1.55(a)(1) (pages 2 to 4 of the Office Action). Applicants respectfully disagree.

The Examiner states that the foreign priority claim filed on March 11, 2002 was not entered because the claim was not filed during the time period set forth in 37 CFR 1.55(a)(1). However, this rule concerns non-provisional U.S. applications, which have different rules than applications filed under 35 USC §371, pursuant to the present application. Applicants assert that the time for filing the priority claim is a deadline set by the PCT in response to the Notification of Missing Requirements Under 35 USC §371 mailed January 24, 2002. Although the executed declaration filed on March 11, 2002 stated the corresponding claim to PCT/GB99/04352, it did not reflect the original foreign priority claim to European patent application No. 98310567.7. However, it was not necessary to claim priority to European patent application No. 98310567.7 because this claim exists in PCT/GB99/04352.

The following is stated in MPEP §1893.03(c):

> To obtain priority in the U.S. national stage application to such applications, the priority must have been timely claimed in the international stage of the international application. See 37 CFR 1.55(a)(1)(ii). If priority was properly claimed in the international stage of the international application, the claim for priority is acknowledged and the national stage application file is checked to see if the file contains a copy of the certified copy of the priority document submitted to the International Bureau.

Applicants also note that the present application is the US national phase of International Application No. PCT/GB99/04352 (published as WO 00/37676), which was

filed on 22 December 1999. International Application No. PCT/GB99/04352 validly claimed priority from European Application No. 98310567.7, which was filed on 22 December 1998. A certified copy of European Application No. 98310567.7 was timely filed during the International phase in accordance with Rule 17.1 PCT. In support of this, Applicants attach a copy of Form PCT/IB/304 issued on International Application No. PCT/GB99/04352.

Finally, Applicants also note the foreign priority data in the Preliminary Amendment filed with the 35 USC §371 application. Although there was a typographical error in the specification amendment, reference to the proper European patent application for priority would indicate that the correct filing date would have been known. This error is corrected herein.

Applicants respectfully request withdrawal of the objection.

II. Objection to the Specification

The specification was objected to because the abstract of the disclosure did not commence on a separate sheet in accordance with 37 CFR §1.52 (b)(4). Applicants amend the specification herewith to address this issue, finding support for the abstract on the filed cover page to the WO 00/37676 publication. Applicants also correct a typographical error in the priority claim submitted in the Preliminary Amendment filed June 21, 2001. One of skill in the art would recognize that this is a typographical error and not new matter, as the cited European Application No. 98310567.7 has a known filing date of December 22, 1998 and is referred to on the Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 USC §371.

No new matter is entered herein.

III. Issues Under 35 USC §112, second paragraph

Applicants address the following issues under 35 USC §112, second paragraph

A. Claims 19 and 20

The Examiner rejects claims 19 and 20 because the terms "bacterial essential protein" and "essential bacterial protein" are allegedly vague and unclear. The Examiner argues that it is not clear whether these terms encompass a protein that is essential to the viability of a particular bacterium or any protein of known or unknown function whose expression *in vivo* is subject to a feedback mechanism.

A person skilled in the art would understand that the essential protein must be a protein that is (a) essential to bacterial viability and (b) associated with a feedback mechanism.

In terms of (a), a person skilled in the art would clearly understand the term "essential" to mean that the protein is vital to the viability of the bacterium. That is the normal meaning of the term, and it has been settled by the courts that claim language generally carries the ordinary meaning of the words in their normal usage in the field of the invention." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1367 (Fed. Cir. 2003). It is also clear to a person skilled in the art that the present invention concerns identifying antibiotics (for example, see page 2, lines 3 to 5 of the specification). They would therefore understand that the assays of the invention involve identifying modulators of proteins that are essential to the viability of a particular bacterium and are therefore capable of killing that bacterium.

In terms of (b), it is clear to a person skilled in the art that the invention concerns identifying regulatory sequences that are affected by feedback mechanisms involving an essential protein (claims 19 and 20) and using these feedback mechanisms to identify antibiotics (claim 23 and page 2, lines 3 to 9). They would therefore understand that the essential protein must be involved in at least one feedback mechanism, otherwise it would not be possible to identify a regulatory sequences affected by a feedback mechanism involving the protein nor would it be possible to identify antibiotics using that feedback mechanism.

A person skilled in the art would also be able to identify suitable essential proteins for use in the invention.

In support of these arguments, Applicants refer the Examiner to the discussion at page 5, line 16 to page 9, line 6 of the application as originally filed. The passage at page 5, lines 16 to 25 discusses the need for the protein encoded by the target gene (*i.e.*, the essential protein) to be one that is essential to bacterial viability and that is associated with a feedback mechanism. The passage at page 5, lines 26 to 29 discusses in general terms the exemplary types of proteins that could be considered to be "essential" in accordance with the invention. Finally, the passage at page 5, line 30 to page 9, line 6, provides several specific examples of essential proteins that may be used in accordance with the invention. Claims 19 and 20 clearly state this, and Applicants therefore assert that these claims are clear and definite. Applicants respectfully request withdrawal of the rejection.

B. Claim 26

The Examiner also rejects claim 26 because the term "its promoter" is allegedly vague and unclear. To further the prosecution of this case, Applicants have replaced this term with "the regulatory sequence".

Applicants respectfully request withdrawal of the rejection.

C. Claim 30

The Examiner further rejects claim 30 because the term "specific inhibition of the essential protein" is allegedly unclear. The Examiner argues that it is not clear whether this term means that the test substance inhibits the essential protein to the exclusion of all others or whether the test substance down-regulates the essential protein directly rather than *via* a feedback mechanism.

A person skilled in the art would clearly understand the term to mean that the test substance inhibits the essential protein to the exclusion of all other proteins. This is the normal meaning of the term "specific inhibition". It is also consistent with the intention of the invention, which is to identify new antibiotics that inhibit specific essential proteins and may therefore be selectively used to treat particular bacteria.

In addition, a person skilled in the art would understand that the manner in which the test substance inhibits the essential protein is irrelevant in the context of the invention. The invention clearly involves the use of a feedback mechanism that is responsive to an alteration in the synthesis or activity of an essential protein to identify which test substances are capable of modulating the essential protein. It does not involve identifying test substances that modulate an essential protein *via* a feedback mechanism. Hence, a person skilled in the art would not interpret the term "specific inhibition" in claim 30 as referring to the manner in which the test substance inhibits the essential protein.

Applicants submit that claim 30 is clear and definite and respectfully request withdrawal of the rejection.

IV. Issues Under 35 USC §112, first paragraph, Enablement

The Examiner rejects claims 19 to 25 and 27 to 30 as lacking enablement. In particular, the Examiner argues that although these claims are enabled for methods involving a candidate regulatory sequence from a bacterial essential protein, the application does not provide enablement for the use of any candidate regulatory sequence linked to a reporter

gene. However, the application does contain a written description of the invention as currently claimed in such full, clear, concise and exact terms as to enable any person skilled in the art to use the invention. In particular, the application does enable a person skilled in the art to carry out the methods of the invention using a candidate regulatory sequence that is not a regulatory sequence of the bacterial essential protein.

The application as originally filed includes considerable disclosure concerning how to carry out the methods of the invention using candidate regulatory sequences that are not regulatory sequences of the essential protein, and Applicants refer the Examiner to pages 15-19 of the originally filed disclosure wherein straightforward yet exemplary techniques that are routine to a person skilled in the art are provided.

As disclosed at page 18, lines 22 to 24, for any given target gene (*i.e.* any given nucleic acid sequence encoding an essential protein), there is a good probability that somewhere in the genome there will be a regulatory sequence whose activity is enhanced or reduced by lack of the target (*i.e.* essential protein) function. Hence, for any particular essential protein, it is likely that a candidate regulatory sequences that is not a regulatory sequence of the essential protein itself can be identified. The disclosure in the application as originally filed allows a person skilled in the art to identify such regulatory sequences in a straightforward manner.

Applicants address each of the *In re Wands* factors in turn.

A. Nature of the invention

The Examiner notes that compounds or constructs must be used to alter the synthesis or activity of the essential protein in such a way as to allow the maintenance or viability of the bacteria until such time as the feedback effect can be monitored by changes in reporter gene expression or differences in gene expression between bacteria in the presence of normal and altered synthesis or activity of the essential protein. This is well within the ability of a person skilled in the art. For instance, the amount of the compound or construct that must be used and the length of time the bacteria must be exposed to them can be determined using straightforward techniques that are routine in the art.

The Examiner also indicates that the invention must be able to identify those substances that give false positive or false negative results by acting directly on the candidate regulatory sequence. A person skilled in the art is capable of doing this based on the information provided in the application as originally filed. For example, in some instances, a

person skilled in the art would know if a particular substance stimulated or inhibited a particular candidate regulatory sequence. In addition, a skilled person can carry out routine control experiments to determine whether or not a particular substance stimulated or inhibited a particular candidate regulatory sequence. This is straightforward and forms part of the normal and routine duties of a person skilled in the art.

B. Breadth of the claims

The Examiner is correct that the claims refer to the use of any bacterial essential protein and any candidate regulatory sequence operably linked to any reporter gene. Example 1 of the application as originally filed demonstrates one exemplary way in which the invention can be carried out. The rest of the application discusses in detail how different embodiments of the invention can be performed. A person skilled in the art is in a position to select appropriate essential proteins, candidate regulatory sequences and reporter genes based on their knowledge of the art and the disclosure in the application as originally filed.

The Examiner cites two specific embodiments that allegedly support the objection of lack of enablement. However, the Examiner has not provided any **evidence** that confirms that a person skilled in the art could not carry out these particular embodiments or that they would not work. In contrast, Applicants submit that a person skilled in the art would be able to carry them out and identify whether or not the regulatory sequence is affected by a feedback mechanism involving the essential protein.

In the Examiner's first embodiment, a person skilled in the art would measure the level of expression of the reporter gene (luciferase) in conjunction with the level of expression of an endogenous bacterial gene that is known to be constitutively expressed at a level that is not affected by the substance used to inhibit RNA polymerase. The change in the level of expression of the endogenous gene would act as a control for the effect of inhibition of RNA polymerase on protein synthesis. By comparing the changes in the level of expression of both the reporter gene and the endogenous gene, a person skilled in the art could determine whether or not the regulatory sequence (CMV promoter) is affected by a feedback mechanism involving the inhibition of RNA polymerase.

In terms of his second embodiment, the Examiner asks whether a decrease in the level of D-alanine associated with the inhibition of D-alanine racemase would affect the function of the reporter gene, luciferase. Without further explanation as to the reasoning behind this question, Applicants require clarification before providing an answer. Applicants assume

that the Examiner is suggesting that the change in metabolism and hence ATP levels associated with a decreased D-alanine level would have an effect on luciferase activity independent of any feedback mechanism. However, the Examiner has not provided any evidence to support this suggestion. In the absence of such evidence, Applicants see no reason why a person skilled in the art could not carry out the methods of the invention using D-alanine racemase and luciferase based on the disclosure in the application as originally filed.

C. Guidance Provided by the Specification/The Existence of Working Examples

Again, the Examiner indicates that the invention is not enabled for candidate regulatory sequences other than those sequences known to be in the feedback circuit, *i.e.* those of the bacteria essential protein itself and, possibly, those proteins with which the bacteria essential protein interacts in essential bacterial processes. However, Applicants disagree for the reasons discussed above and note that the courts have already found that it is unnecessary to teach all potential embodiments, as disclosure of well-known techniques or scientific principles to those of skill in the art is not required. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBC v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

D. Working Examples in the Literature

The Examiner refers to a document by Neumann *et al.* (Journal of Basic Microbiology, 1997; 37(1): 35 to 69). This document is one of many documents published before the priority date of the present application that concerns using recombinant DNA technology in bacteria. It is clear from this document that the level of skill of a person skilled in the art of using recombinant DNA technology in bacteria is very high. Hence, a person skilled in the art would have a large amount of general knowledge and experience in genetically modifying bacteria and carrying methods in bacteria. It would be straightforward for such a person to carry out the methods of this invention using that knowledge and experience in combination with the disclosure in the application as originally filed, and Applicants respectfully note that the courts have determined that it is not necessary that a patent applicant test all the embodiments of his invention. *Amgen Inc. v. Chugai*

Pharmaceutical Co., Ltd., 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Section 112 requires simply that the patent applicant provide a disclosure which sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213.

E. Predictability in the Art

The Examiner cites an article by Allsop *et al.* (Current Opinion in Biotechnology, 1998; 9: 637 to 642) that states that the use of expression profiling for functional analysis is at an early stage. Even if the process of assessing the level of expression of various genes in various diseases in order to identify which genes are associated with which diseases was at an early stage at the priority date of the present application, Applicants fail to see the relevance of this to the present application.

The invention concerns identifying feedback mechanisms involving bacterial essential proteins and using those feedback mechanisms to identify possible antibiotics. The present invention does not concern identifying genes associated with pathogenic processes using expression profiling.

As Applicants have discussed above, recombinant DNA technology in bacteria was advanced even at the priority date of the present application. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), and guidance is not necessary to those skilled in the art, particularly when it is well-recognized that the skill in the art of molecular biology is quite high (*Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986).

F. Amount of Experimentation Necessary

Applicants disagree with the Examiner that a great deal of experimentation would be required to reduce the scope of the invention to practice. The application as originally filed provides considerable disclosure on how to practice the invention, particularly using candidate regulatory sequences that are not necessarily the promoter of the bacteria essential protein. A person skilled in the art could use this disclosure in combination with their common general knowledge to carry out the methods as presently claimed using routine techniques in a straightforward manner.

Even if experiments are necessary, a considerable amount of routine experimentation is permissible, especially where the Appellants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976).

In fact, time-consuming experiments are acceptable if the type of experimentation is standard in the art. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Yet further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985); *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicants therefore submit that all of the claims are enabled and respectfully request withdrawal of the rejection.

V. Issues Under 35 USC §112, first paragraph, Written Description

The Examiner rejects claims 23 to 30 as failing to comply with the Written Description requirement. In essence, the Examiner does not believe that the inventors had possession of the invention claimed in claims 23 to 30 at the time the application was filed.

In contrast to the opinion of the Examiner, Applicants contend that the application as originally filed does provide structural information concerning the test substances and the bacteria essential proteins that can be used in the method of claim 23. The passage at page 11, line 22 to 25 discusses suitable exemplary test substances. As discussed above, the passage at page 5, lines 26 to 29 discusses suitable exemplary bacterial essential genes in general terms, while the passage at page 5, line 30 to page 9, line 6 provides specific examples of suitable exemplary bacteria essential proteins.

Example 1 discloses one exemplary way in which a modulator of a bacteria essential protein can be identified in accordance with the invention. It is reasonable to predict that other modulators can be identified for other bacterial essential proteins in accordance with claim 23. As Applicants have discussed above, it would be straightforward for a skilled person to do this. In particular, the application as filed gives guidance on the types of modulator and the different bacteria essential proteins that can be used. Applicants therefore submit that the inventors had possession of the claimed invention at the time the application was filed and that the application satisfies the Written Description requirement. Applicants respectfully request withdrawal of the rejection.

VI. Issues Under 35 USC §102

The Examiner rejects claims 19 to 20, 23 to 26, 28 and 30 as being anticipated by Neumann *et al.* (Journal of Basic Microbiology, 1997; 37(1): 35 to 69). However, Applicants respectfully disagree.

The invention concerns identifying antibiotics (page 1, lines 4 to 6; page 2, lines 3 to 9 and 24 to 28; page 3, lines 29 to 31; page 12, lines 2 to 4; and page 14, lines 23 to 25 of the application as originally filed). This is done by identifying feedback mechanisms that involve an essential protein (claims 19 and 20). Those feedback mechanisms are then used to identify modulators of the essential protein that can be used as antibiotics (claim 23).

In contrast, the paper by Neumann *et al.* concerns studying gyrase expression to investigate the regulation of DNA supercoiling *in vivo* (abstract). In order to do this, the authors generate strains of bacteria in which gyrase regulatory sequences, gyrA and gyrB, are fused to a reporter gene, lacZ (abstract and last paragraph of the introduction on page 54). The resulting strains were then used to evaluate known inhibitors of gyrase activity, such as quinolones and coumarins (Figures 2, 2B, 3, 3B and 4).

Hence, the document by Neumann *et al.* does not disclose a method for identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein (claims 19 and 20). The document does not refer to identifying particular regulatory sequences; neither does it mention feedback mechanisms.

In addition, the document by Neumann *et al.* does not disclose the use of regulatory sequences and feedback mechanisms to screen for and identify new modulators of the essential protein (claim 23). It does not disclose the identification of any new modulators of

gyrase function but instead discusses the evaluation of known gyrase inhibitors. The document certainly does not disclose identifying new antibiotics.

Applicants therefore submit that none of the current claims are anticipated and respectfully request withdrawal of the rejection.

VII. Conclusion

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response other than the fee for Petition for Extension of Time of Three Months. However, if another fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02222US0 from which the undersigned is authorized to draw.

Dated: July 27, 2006

Respectfully submitted,

By _____

Melissa L. Sistrunk
Registration No.: 45,579
FULBRIGHT & JAWORSKI L.L.P.
Fulbright Tower
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
(713) 651-5151
(713) 651-5246 (Fax)
Agent for Applicant

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ELLIS-JONES, Patrick George Armine
J.A. Kemp & Co.
14 South Square
Gray's Inn
London WC1R 5LX
ROYAUME-UNI

J. A. KEMP & Co
- 7 APR 2000
Action by PEOTSER

Date of mailing (day/month/year) 28 March 2000 (28.03.00)	
Applicant's or agent's file reference N.78329A	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/04352	International filing date (day/month/year) 22 December 1999 (22.12.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 22 December 1998 (22.12.98)
Applicant ISIS INNOVATION LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
22 Dece 1998 (22.12.98)	98310567.7	EP	23 Marc 2000 (23.03.00)

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)

003194599